The Evolving Landscape of Chronic Lymphocytic Leukemia

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Disclosures

• Consulting fees from Gilead, Pharmacyclics, Infinity, Amgen, Juno, Amgen, Incyte
B-cell CLL

- Most common leukemia
- 15,000 new cases annually, 4300 deaths
- Median age is 70 years
- Slight male predominance
- Familial risk
  - 13% of patients have an affected 1st degree family members
  - Relative risk 7.5x
Case Presentation

- A 66yo man presents for an annual physical.
- A CBC is notable for a WBC count of 25,000/uL with an absolute lymphocyte count of 15,000/uL. Other counts are normal.
- He is without symptoms
- Physical exam is normal without adenopathy or splenomegaly.
What is the optimal diagnostic procedure at this time?

1. Bone marrow aspiration and biopsy
2. Peripheral Blood for flow cytometry
3. Peripheral blood for cytogenetics analysis
4. PET/CT scan
5. Serum protein electrophoresis
Treatment versus Observation

- Indications for therapy
  - Constitutional Symptoms
  - Local symptoms
  - Progressive/significant cytopenias
  - Symptomatic splenomegaly
  - Bulky lymphadenopathy
  - Hypogammaglobulinemia with recurrent infections
  - Autoimmune cytopenias unresponsive to steroids

Dighiero, et al. NEJM 1998
**Immunophenotype**

- Dim surface CD20 and light chain
- Co-expression of CD5, CD23 and CD43
- Cyclin D1 negative
Monoclonal B-cell Lymphocytosis

- Clonal lymphocytosis < 5000/uL without adenopathy, splenomegaly, cytopenias
- Present in 5% of healthy adults
- Carries a 15% risk of having progressive lymphocytosis meeting the definition of CLL, and only a 7% risk of developing CLL necessitating treatment

Rawstron, et al. NEJM 2008
Flow Cytometry is consistent with CLL and ALC is 8500. What diagnostic test would most confer an adverse prognosis?

1. Elevated Lactate Dehydrogenase
2. FDG-avid disease on PET-CT
3. Cytogenetics with deletion of 13q
4. Cytogenetics with deletion of 11q
5. Cytogenetics with deletion of 17p
### Clinical Staging: Rai and Binet

**RAI STAGING SYSTEM**

<table>
<thead>
<tr>
<th>Stage*</th>
<th>Criteria</th>
<th>Median Survival (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O (low-risk)</td>
<td>Lymphocytes $&gt; 15 \times 10^9$ /L, Bone marrow $&gt; 40%$ Lymphocytes</td>
<td>$&gt; 10$</td>
</tr>
<tr>
<td>I and II (intermediate-risk)</td>
<td>Blood and bone marrow lymphocytosis, lymphadenopathy, liver or spleen enlargement</td>
<td>$6$</td>
</tr>
<tr>
<td>III and IV (high-risk)</td>
<td>Blood and bone marrow lymphocytosis plus anemia (hemoglobin $&lt; 11$ g/dL) or thrombocytopenia (platelets $&lt; 100 \times 10^9$/L)</td>
<td>$2$</td>
</tr>
</tbody>
</table>

**BINET STAGING SYSTEM**

<table>
<thead>
<tr>
<th>Group*</th>
<th>Criteria</th>
<th>Median Survival (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No anemia or thrombocytopenia, less than three of the following five areas involved: axillary, inguinal, cervical (unilateral or bilateral), lymphadenopathy, liver, spleen</td>
<td>$9$</td>
</tr>
<tr>
<td>B</td>
<td>No anemia or thrombocytopenia; three or more involved areas</td>
<td>$5$</td>
</tr>
<tr>
<td>C</td>
<td>Anemia (hemoglobin $&lt; 10$ g/dL) or thrombocytopenia (platelets $&lt; 100 \times 10^9$/L)</td>
<td>$2$</td>
</tr>
</tbody>
</table>

* Autoimmune hemolytic anemia and thrombocytopenia are independent of stage or group.
FISH and prognosis

**Table 1. Incidence of Chromosomal Abnormalities in 325 Patients with Chronic Lymphocytic Leukemia.**

<table>
<thead>
<tr>
<th>Aberration</th>
<th>No. of Patients (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>13q deletion</td>
<td>178 (55)</td>
</tr>
<tr>
<td>11q deletion</td>
<td>58 (18)</td>
</tr>
<tr>
<td>12q trisomy</td>
<td>53 (16)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>23 (7)</td>
</tr>
<tr>
<td>6q deletion</td>
<td>21 (6)</td>
</tr>
<tr>
<td>8q trisomy</td>
<td>16 (5)</td>
</tr>
<tr>
<td>t(14q32)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>3q trisomy</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Clonal abnormalities</td>
<td>268 (82)</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>57 (18)</td>
</tr>
</tbody>
</table>

*One hundred seventy-five patients had one aberration, 67 had two aberrations, and 26 had more than two aberrations.*
For the 66yo patient with stage 0 CLL, the optimal initial approach is?

1. Observation alone
2. Fludarabine-Cyclophosphamide-Rituximab (FCR)
3. Bendamustine-Rituximab (BR)
4. Obinutuzimab-Chlorambucil
5. Ibrutinib monotherapy
Treatment versus Observation

- Indications for therapy
  - Constitutional Symptoms
  - Local symptoms
  - Progressive/significant cytopenias
  - Symptomatic splenomegaly
  - Bulky lymphadenopathy
  - Doubling time < 6 months
  - Autoimmune cytopenias unresponsive to steroids

Dighiero, et al. NEJM 1998
You observe for 5 years

Patient develops progressive fatigue. Lymphocytosis is 82,000, hematocrit 30% and platelets 65,000. He is now 72 years old. Repeat FISH shows only 13q-deletion. Other medical conditions include diabetes mellitus, atrial fibrillation, and chronic renal insufficiency. Optimal management now is:

1. Ongoing observation
2. Fludarabine-Cyclophosphamide-Rituximab (FCR)
3. Bendamustine-Rituximab (BR)
4. Obinutuzimab-Chlorambucil
5. Ibrutinib monotherapy
FCR versus FC: *The GCLLSG CLL8 trial*

- Untreated CLL requiring therapy
- FCR vs. FC for 6 cycles
- N=817
- ORR 90% vs 80%
- CRR 44% vs 22%

FCR versus FC: Overall Survival Analysis

The GCLLSG CLL8 trial

# Bendamustine-Rituximab

<table>
<thead>
<tr>
<th>N</th>
<th>117</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>64</td>
</tr>
<tr>
<td>ORR</td>
<td>88%</td>
</tr>
<tr>
<td>CRR</td>
<td>23%</td>
</tr>
<tr>
<td>Median EFS</td>
<td>34 months</td>
</tr>
</tbody>
</table>

## Toxicity
- Grade 3-4 ANC: 6.5%
- Grade 3-4 PLT: 6.1%
- Grade 3-4 infection: 5%
- Death: 2.6%

FCR vs. BR: CLL10

**Design**

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Randomization

**FCR**
- Fludarabine 25 mg/m² i.v., days 1-3
- Cyclophosphamide 250 mg/m², days 1-3,
- Rituximab 375 mg/m² i.v. day 0, cycle 1
- Rituximab 500 mg/m² i.v. day 1, cycle 2-6

**BR**
- Bendamustine 90mg/m² day 1-2
- Rituximab 375 mg/m² day 0, cycle 1
- Rituximab 500 mg/m² day 1, cycle 2-6

Eichhorst et al. Proc ASH 2014
FCR vs. BR: CLL10

Progression-free survival by age group

Patients ≤ 65 years: \( P < 0.001 \)

- FCR: 53.6 months
- BR: 38.5 months

Patients > 65 years: \( P = 0.170 \)

- FCR: not reached
- BR: 48.5 months

Eichhorst et al. Proc ASH 2014
**FCR vs. BR: CLL10**

Overall survival

OS at 36 months:
- FCR 90.6%
- BR 92.2%

$P = 0.897$

Eichhorst et al. Proc ASH 2014
## Randomized Trials of Initial CLL Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Median Age</th>
<th>Median CIRS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCR vs. FC</td>
<td>408</td>
<td>61</td>
<td>1</td>
</tr>
<tr>
<td>FCR vs. BR</td>
<td>561</td>
<td>61</td>
<td>2</td>
</tr>
<tr>
<td>Benda vs. Chlorambucil</td>
<td>319</td>
<td>63</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Obinutuzumab (GA101)

Increased Direct Cell Death
Type II versus Type I antibody

Upper CDC
Type II versus Type I antibody

Enhanced ADCC
Glycoengineering for increased affinity to FcγRIIIa

ADCC, antibody-dependent cell-mediated cytotoxicity
CDC, complement-dependent cytotoxicity
• Median age 73, Median CIRS score 8
  • GA101: 1,000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
  • Rituximab: 375 mg/m² day 1 cycle 1, 500 mg/m² day 1 cycles 2–6, every 28 days
  • Clb: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
  • Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb
CLL11 results

Goede et al. NEJM 2014.
Initial treatment for CLL

- No 17p deletion
  - Young/fit patients: Fludarabine-cyclophosphamide-rituximab
  - Elderly fit patients: Bendamustine-rituximab
  - Elderly unfit patients or very elderly: Chlorambucil-Obinutuzumab

- 17p-deletion
  - Conventional chemoimmunotherapy strategies work poorly
Bruton’s Tyrosine Kinase (Btk)
A Critical B-Cell Signaling Kinase

- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- Bruton’s Tyrosine Kinase (Btk) is an essential element of the BCR signaling pathway
- Inhibitors of Btk block BCR signaling and induce apoptosis
### Ibrutinib for CLL

<table>
<thead>
<tr>
<th></th>
<th>Treatment naive</th>
<th>Relapsed/refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>101</td>
</tr>
<tr>
<td>Median age</td>
<td>71 (range 65-84)</td>
<td>64 (37-82)</td>
</tr>
<tr>
<td>Rai stage III-IV</td>
<td>17 (55%)</td>
<td>58 (57%)</td>
</tr>
<tr>
<td>Del 17p / Del 11q</td>
<td>2 (6%) / 1 (3%)</td>
<td>34 (34%) / 35 (35%)</td>
</tr>
<tr>
<td>Median CrCl, mL/hr</td>
<td>67</td>
<td>81</td>
</tr>
<tr>
<td>Median prior therapy</td>
<td>-</td>
<td>4 (range 1-12)</td>
</tr>
</tbody>
</table>

Ibrutinib Response Pattern

Hemoglobin and Platelets

Best Overall Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Treatment naive</th>
<th>R/R</th>
<th>R/R with del 17p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>84%</td>
<td>90%</td>
<td>79%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>23%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>55%</td>
<td>80%</td>
<td>65%</td>
</tr>
<tr>
<td>Partial Response + lymphocytosis</td>
<td>6%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10%</td>
<td>4%</td>
<td>12%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0%</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Ibrutinib in CLL: PFS and OS

**Progression-Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Treatment Naive</th>
<th>R/R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 month PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>R/R</td>
<td>69%</td>
<td></td>
</tr>
</tbody>
</table>

**Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Treatment Naive</th>
<th>R/R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 month OS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>R/R</td>
<td>79%</td>
<td></td>
</tr>
</tbody>
</table>

Survival by FISH

### Progression-Free Survival

- **No 17p-/11q-**
  - 30 month PFS: 87%
- **11q-**
  - 30 month PFS: 74%
- **17p-**
  - 30 month PFS: 48%

### Overall Survival

- **No 17p-/11q-**
  - 30 month OS: 90%
- **11q-**
  - 30 month OS: 85%
- **17p-**
  - 30 month OS: 65%

Notable Toxicities

- Diarrhea
- Atrial Fibrillation
- Bruising and Bleeding – *relatively contraindicated in patients on therapeutic anticoagulation*
Upfront Ibrutinib

- Eligibility
  - Age ≥ 65 years
  - Requirement for therapy

- 29 patients
  - Median age 71
  - Rai III-IV 44%
  - 17p- 6%

PI3 Kinase pathway and B cell malignancies

- **T-cell**
- **CD40**
- **BCR**
- **PI3K**
- **AKT**
- **JAK**
- **TRAF6**
- **LYN/SYK**
- **PLCγ1**
- **PLCγ2**
- **BTK**
- **GSK-3**
- **mTOR**
- **p70s6k**
- **elf4E**
- **NF-κB pathway**
- **IL-6R**
- **BAFFR**
- **CXCR5**
- **PI3K Pathway Drives**
  - Proliferation ↑
  - Cell survival ↑
  - Trafficking ↓

**Stromal cell**
- **IL-6**
- **BAFF**
- **CXCL13**
Idelalisib: Phase 1 efficacy

Best On-Treatment Change in Tumor Size

-100
-75
-25
0
-50*
25
50
75
100

MCL (N=21)
iNHL (N=30)
CLL (N=54)

Inevaluable (patients without a follow-up tumor assessment)

* Criterion for response [Cheson 2007, Hallek 2008]

Kahl, ASH 2010, #1777; Furman, ASH 2010 (courtesy Dr. Kahl)
Idelalisib-Rituximab vs. Rituximab in Elderly Relapsed CLL

- Eligibility
  - Decreased renal function
  - Cytopenias
  - Major comorbidities
- N=220
- Median age 71
- Rai 3-4 64%
- 17p- 43%
- Median 3 prior tx

*Outcome independent of 17p-

Idelalisib Toxicity

- Diarrhea
- Colitis
- Pneumonitis
- AST/ALT Elevation
- Infection
- Fatigue
- Fever
- Nausea
- Rash
- Cytopenias
3 years after obinutuzumab-chlorambucil, your patient again has symptomatic progression and cytopenias

He is now 74 years old. He remains on warfarin for atrial fibrillation. For treatment, you recommend:

1. Ibrutinib
2. Idelalisib-rituximab
3. Bendamustine-Rituximab
4. Rituximab
5. Fludarabine-cyclophosphamide-rituximab
The intrinsic apoptotic pathway is universally dysregulated in CLL/SLL due to an overexpression of anti-apoptotic proteins such as BCL-2.

ABT-199 is a selective, potent, orally bioavailable BCL-2 inhibitor.
**Response**

**Lymphocytosis**

**Nodal disease**

<table>
<thead>
<tr>
<th>Responses</th>
<th>All n (%), n = 78</th>
<th>del (17p) n (%), n = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>60 (77)</td>
<td>15 (79)</td>
</tr>
<tr>
<td>Complete response*</td>
<td>18 (23)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Partial response</td>
<td>42 (54)</td>
<td>10 (53)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (13)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>2 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>D/C Prior to assessment</td>
<td>6 (8)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

*11 of 18 patients with CR assessed for MRD by 4 color flow, 7 of whom had no detectable MRD were assessed for MRD.*
• Targeted therapies are transforming the face of CLL therapy

• Currently, chemoimmunotherapy (FCR, BR, Obin-Chl) remains the standard initial therapy for most patients, with choice of regimen based on age, fitness and comorbidities

• Ibrutinib is an upfront treatment option for 17p- disease

• Ibrutinib and Idelalisib-rituximab are highly active in the relapsed/refractory setting, including in 17p- patients, and have unique toxicity profiles

• Ibrutinib favored at 1\textsuperscript{st} relapse based on risk/benefit ratio, but consider idelalisib preferentially in anticoagulated patients
Conclusions (2)

- Ongoing randomized trials will likely demonstrate ibrutinib as a standard upfront treatment option in most patients
  - Ibritunib vs. Chlorambucil
  - Ibrutinib vs. Ibrutinib-Rituximab vs. BR (Alliance)
  - Ibrutinib-Rituximab vs. FCR (ECOG)

- Additional BTK and PI3K inhibitors are in development

- ABT199 (venetoclax) is a BH3-minmomic inhibiting BCL2 with dramatic activity and will soon join our treatment armamentarium